Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL) Workshop

Sponsored by the U.S. Food and Drug Administration and the American Society of Clinical Oncology (ASCO)
Co-Chairs Dr. Stephen Hunger and Dr. Gregory Reaman
April 18, 2012

AGENDA

This workshop will provide a forum for discussion of extending the qualification of minimal residual disease (MRD) detection as a prognostic biomarker to an efficacy/response biomarker in evaluating new drugs for the treatment of Acute Lymphoblastic Leukemia (ALL).

8:00 a.m.	Welcome and Workshop Objectives	**Gregory Reaman, M.D.** Associate Director Office of Hematology and Oncology Products (OHOP) Office of New Drugs, CDER, FDA **Stephen Hunger, M.D.** Ergen Family Chair in Pediatric Cancer and Director, Center for Cancer and Blood Disorders Children's Hospital Colorado Chief, Section of Pediatric Hematology/Oncology/Bone Marrow Transplantation Professor of Pediatrics, Univ. of Colorado School of Medicine

<u>REGULATORY BACKGROUND AND CONSIDERATIONS</u>

8:05	Clinical Benefit for New Drug Approvals	**Albert Deisseroth, M.D., Ph.D.** Medical Team Leader Division of Hematology OHOP, OND, CDER, FDA
8:15	*In vitro* Diagnostics- Role in Prognostic and Efficacy Biomarker Assessment	**Elizabeth Mansfield, Ph.D.** Director, Personalized Medicine Staff Office of *In vitro* Diagnostic Device Evaluation and Safety (OVI), CDRH, FDA
8:35	Biomarker Qualification: the FDA Perspective	**Marc Walton, M.D., Ph.D.** Associate Director Office of Translational Sciences
8:55	Clarifying Questions to the Presenters	

Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL) Workshop

AGENDA (continued)
April 18, 2012

EXPANDING THE ROLE OF MRD FROM PROGNOSTIC TO EFFICACY BIOMARKER: A SURROGATE PREDICTING CLINICAL BENEFIT

MRD as a Prognostic Biomarker and Potential Surrogate in Select Populations

9:05	Adults with ALL: The GMALL experience	**Nicola Gökbuget, M.D.** Head of Study Center, University Cancer Center, Goethe University Hospital Department of Medicine II Hematology/Oncology Frankfurt, Germany

Relapsed ALL: Does End-Induction MRD Predict 1 yr or 2 yr EFS –

9:25	The COG AALLO1P1 experience	**Elizabeth Raetz, M.D.** Associate Professor; Fellowship Dir of Pediatric Hematology/Oncology Department of Pediatrics (Oncology Division) NYU Pediatric Hematology Oncology

MRD as a Surrogate Endpoint for Efficacy Evaluation of New Drugs in Very High Risk ALL

9:45	Prognostic Significance of MRD in Ph+ All: The COG Experience	**Stephen Hunger, M.D.** Children's Hospital Colorado
10:05	*Break*	
10:20	MRD as a Prognostic Marker in VHR ALL	**Andrea Biondi, M.D.** Professor of Pediatrics at the Faculty of Medicine and Surgery, and Director of the Department and the School of Pediatrics, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy

Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL) Workshop

AGENDA (continued)
April 18, 2012

STATISTICAL CONSIDERATIONS FOR SURROGATE ENDPOINTS

10:40	Can a critical threshold value of early MRD assessment be a surrogate for OS/EFS in ALL?	**Meenkashi Devidas, Ph.D.** Research Assoc. Professor, Dept. of Biostatics Co-Director, Children's Oncology Group Statistics and Data Center, University of Florida **Maria Grazia Valsecchi, Ph.D.** Professor of Medical Statistics, Centre of Biostatics for Clinical Epidemiology, Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy **Mark Rothmann, Ph.D.** Office of Translational Science Office of Biometrics/DBV Office of New Drugs, CDER, FDA

Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL) Workshop

AGENDA (continued)
April 18, 2012

TECHNICAL APPROACHES TO MRD ASSESSMENT: SENSITIVITY, FEASIBILITY, AND COMPARABILITY

11:10	Technical, economical, and validation - QC considerations for multicenter MRD assessment as an efficacy endpoint in ALL	**Jacques J.M. van Dongen, M.D.** Department of Immunology Erasmus Medical Center, University Medical Center Rotterdam, the Netherlands
11:30	Flow cytometry in MRD Assessment	**Brent Wood, M.D.**, **Ph.D**. Department of Laboratory Medicine University of Washington
11:50	Molecular quantification of MRD	**Gianni Cazzaniga, Ph.D.** Senior Scientist, M. Tettamanti Research Center, Department of Pediatrics, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy

12:10 Clarifying Questions to the Presenters and Group Discussion

12:25 *Lunch*

QUESTIONS TO WORKSHOP PARTICIPANTS, DECISIONS, AND SUMMARY

1:25 Questions 1-4

2:30 *Break*

QUESTIONS TO WORKSHOP PARTICIPANTS, DECISIONS, AND SUMMARY

2:45 Questions 5-9

3:45 Wrap-up/Next Steps

4:00 *Adjourn*

Questions for Workshop Panelists

1. Do the data demonstrating the predictive ability of MRD warrant the designation of a critical threshold value for end-Induction MRD as a surrogate for event free and (EFS) overall survival (OS) in ALL?

    a. Please address the need for a meta-analysis of current datasets to justify this.
    b. Please discuss potential trial designs which would isolate the efficacy of a new agent when used as a component of a known active, multi-drug regimen.

2. Would the use of MRD as a surrogate endpoint be best suited to clinical trials evaluating new drugs for specific clinical/biologic subtypes of ALL (selected patient populations)? Which subgroups would be most appropriate?

3. Since current risk adjusted treatment strategies utilize end-Induction MRD to determine therapy, what study design (s) could be considered incorporating MRD as an endpoint?

4. Does end- Induction MRD in the setting of relapsed ALL have prognostic significance and predict long term EFS or OS following induction of CR2? Could MRD be a surrogate endpoint for clinical trials of new drugs in relapsed/refractory ALL?

MRD Workshop – Questions for Technical Discussion

5. What is the necessary degree of concordance between FCM and RQ-PCR in designating critical MRD thresholds and should a single technology platform be used?

6. How will analytical performance of MRD levels be assessed for biomarker qualification?

    a. How can analytical performance be determined during biomarker qualification and what panel(s) will be used?
    b. Is analytical validation sufficient or is clinical validation a requirement? Describe how clinical validity can be defined, particularly if LAIPS may not identify all phenotypes.

7. Considering panel composition, reagent optimization, post acquisition analytic methods, data reporting, clinical thresholds, etc., what are the challenges, merits and clinical implications of creating uniform and standardized clinical flow cytometry and molecular methods for MRD analysis?

8. What is the minimum number of markers to include in an MRD panel and what percent of LAIPs will be identified with it? Discuss the issue of clinical sensitivity versus panel size.

9. Irrespective of which standardized technology platform(s) is/are used for determination of critical MRD threshold values, should testing be centralized, regionalized, and if performed at a local institutional level, certified/audited? Controls and proficiency testing are regarded as essential in order to demonstrate that results across sites are comparable.